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THE THERAPEUTIC USE OF SINGLE DOSES OF TOTAL BODY RADIATION*†

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RADIATION therapy and chemotherapy are recognized as having equivalent or complementary roles in the treatment of certain types of cancer. In general, radiation has been restricted to the treatment of relatively localized manifestations, and chemotherapy has been used when the disease is more widely disseminated. There has been limited use of total body irradiation in the treatment of generalized neoplastic disease. In the Heublein technique[8,11] low intensity, continuous irradiation was used to administer doses up to 450 roentgens in three weeks. Hempelmann *et al.*,[6] writing on the acute radiation syndrome, noted that 100 r of 200 kv. roentgen rays could be delivered to the entire body of the patient without causing symptoms of any sort. Recently, Osgood and Seaman[12] have advocated a "titration technique" in the treatment of leukemia in which doses of 10–25 r were given to the whole body at regularly spaced intervals. In a scrupulous effort to avoid radiation sickness and bone marrow depression, a conventional technique employing total body irradiation for the treatment of polycythemia utilizes doses of 25 r repeated to a total of 300 r in three weeks. From these different techniques, using varying formulae of intensity, dose, and time, it is difficult to assess the tolerance to whole body irradiation.

Perhaps the most extensively employed chemotherapeutic agent has been nitrogen mustard, methyl bis (beta chloroethyl) amine (HN_2). This agent has been used in almost every form of malignant disease and in some benign conditions such as rheumatoid arthritis.[4] It has become the standard form of therapy for generalized Hodgkin's disease. In accepted clinical doses, nitrogen mustard produces a sharp systemic reaction and the patient is heavily sedated before treatment to control nausea and vomiting. Hematopoietic depression is constant, and severe leukopenia and thrombocytopenia is a recognized hazard of repeated courses. These toxic side effects have not been a deterrent to common use although they exceed the severity of radiation sickness.

In 1950 Gellhorn and Collins[5] undertook a comparative study of two groups of patients with Hodgkin's disease, one of which had received radiation and nitrogen mustard in alternating therapeutic courses, and the other radiation therapy alone. It could not be shown that the addition of nitrogen mustard to the therapy regimen increased survival time but the drug was regarded as a useful adjunct to the extent that it reduced the time under treatment and the amount of radiation required. If nitrogen mustard did not increase survival time beyond that obtained with radiation therapy alone, its only purpose was to offer the convenience of a systemic approach to treatment. It seemed possible that higher doses of total body irradiation might offer equal benefit with side effects of less severity. Phillips *et al.*[13] had studied the application of massive doses of radiation to liver for metastatic disease. Court Brown[3] had reported observations on symptoms associated with single therapeutic doses of roentgen radiation to large portions of the body, and to the whole body.

In a previous report the tolerance to total body irradiation was compared with the effects of nitrogen mustard and triethylene

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melamine.[10] Total body irradiation in single doses up to 150 r was less depressing for hematopoiesis and patients were free of malaise that was constantly associated with these drugs. These observations suggested that a therapeutic effect of total body irradiation might be sought in patients having disseminated disease ordinarily treated by a variety of chemotherapeutic agents.

In the present series of patients, dose has been expressed in roentgens on skin and measurements were made with a Victoreen chamber on the surface of a pressdwood phantom at treatment distance. Court Brown and Mahler[2] reported their series of single exposures to radiation in terms of energy absorbed or integral dose. There was some necessity for this in that their patients received treatment to varying portions and proportions of the body, and dose in roentgens would have no direct correlation with tolerance of the individual to radiation. For purposes of duplication, dose on skin represents the simplest expression of exposure to radiation. Boden and Cohen[1] have called attention to variations that exist in measuring dose in different institutions and it appears that no accuracy would be gained in the assumptions and calculations necessary for determining integral dose for total body irradiation.

In addition to the usual blood examinations, radioactive iron tracer studies were carried out because of the work of Hennessy and Huff[7,9] indicating a quantitative relation between the utilization of injected iron for hemoglobin production, and dose of total body irradiation, in rats. The half time of disappearance of radioiron from the blood is normally one to two hours for humans. Prolongation of the half time indicates decreased hemoglobin formation and may be useful as an early and sensitive index of change in guiding further therapy.

REPORT OF CASES

CASE I. B.L. (AR-8422) A male, aged seventy-three, developed generalized lymphadenopathy in November, 1951, and a diagnosis of "lymphoma" was made by biopsy. Treatment was withheld because of lack of symptoms. In March, 1953, the patient was admitted to the hospital because of 20 pounds weight loss, pain in left shoulder, and edema of left upper extremity. There was extensive lymphadenopathy with nodes as large as 5 cm. in diameter; liver extended 5 cm. below the costal margin.

On March 23, 1953, the patient received 75 r (skin dose) total body irradiation anteriorly and 75 r posteriorly (250 kv., constant potential, half-value layer 2.3 mm. Cu, target skin distance 360 cm.). In the first forty-eight hours the patient was anorexic but there was no nausea, vomiting or diarrhea. On the third day the patient's appetite returned and the lymph nodes began to diminish in size. On May 12, 1953, he was discharged from the hospital and returned to work. Later in the month he received 600 r tissue dose to the mediastinum in eight days on an out-patient basis. In December, 1953, in another city, he underwent partial gastric resection for ulcer of the lesser curvature. At present he is convalescing satisfactorily.

Laboratory data during the period associated with total body irradiation were as follows:

	Initial	*Low*	*Final (11 mo.)*
Hb.	11.9 gm.	7.6 gm. @ 5 wk.	11.0 gm.
R.B.C.	4,300,000	1,700,000 @ 5 wk.	3,800,000
W.B.C.	29,000	4,000 @ 8 wk.	10,000
Platelets	240,000	110,000 @ 8 wk.	148,000
Iron turnover half time	1.3 hr.	4.2 hr. @ 23 days	0.4 hr.

Differential white cell count became normal at eight weeks.

CASE II. W.D. (AJ-6024) A seventy-two year old white male was admitted for repair of inguinal hernia and was discovered to have a white blood cell count of 155,000. The differential white cell count was consistent with chronic myelogenous leukemia. Liver and spleen were palpably enlarged. The blood pressure was 200/90. He had lost 20 pounds in

weight in the past year. On June 24, 1953, he received 150 r (skin dose) total body irradiation to the anterior aspect of body (250 kv., half-value layer 2.3 mm. Cu, target skin distance 360 cm.). There was mild anorexia on the following morning but his appetite was normal by noon. There was no nausea, vomiting or malaise. Liver and spleen gradually diminished in size and were no longer palpable after two weeks.

Laboratory data during treatment and follow-up were as follows:

	Initial	*Low*	*Final (8 mo.)*
Hb.	10.1 gm.	7.5 gm. @ 4 wk.	11.0 gm.
R.B.C.	3,800,000	2,900,000 @ 4 wk.	3,100,000
W.B.C.	193,000	11,000 @ 3 mo.	98,000
Platelets	265,000	225,000 @ 1 wk.	216,000
Iron turnover half time	0.6 hr.	2 hrs. @ 1 day	1.5 hr.

Differential white cell count became normal at three months.

CASE III. J.B.C. (AX-7573) A fifty-one year old white male was admitted to the hospital on September 10, 1953, with a biopsy diagnosis of multiple myeloma. He had been paraplegic and incontinent of urine and feces for three weeks; he had developed a large sacral decubitus ulcer, his general condition was poor and he complained of severe dorsal and lumbar back pain. He was placed on a Foster frame and daily care was given to the decubitus ulcer, which showed slow improvement.

On September 15 he was given 200 r (skin dose) total body irradiation (250 kv., peak, half-value layer 2.3 mm. Cu, target skin distance 360 cm.). There was mild nausea of one day's duration; there was no vomiting. Because there was only partial loss of tactile sensation accompanying the motor paralysis, the total body irradiation was followed two weeks later by local roentgen therapy to the spine. A tissue dose of 675 r was delivered in ten days to vertebral bodies from C-4 to S-1. No change was detected in the neurologic findings; however, narcotic requirements for pain were considerably less than before treatment. The patient's condition gradually deteriorated and he died on Oct. 28, 1953. No autopsy was obtained.

Laboratory data during the period associated with total body irradiation were as follows:

	Initial	*Low*	*Final (6 wk.)*
Hb.	11.0 gm.	5.7 gm. @ 4 wk.	7.5 gm.
W.B.C.	8,500	4,050 @ 5 wk.	5,500
Platelets	240,000 –	220,000 @ 4 wk.	250,000

There was no change in differential white blood cell count.

CASE IV. O.B. (Y-13361) This white female, aged fifty-eight, gave a six year history of backache radiating to the legs. In April, 1948, she received roentgen therapy to a destructive lesion in the body of the second lumbar vertebra with diminution of pain. In 1951 a second course of therapy was given to this area, and in January, 1952, a third course. On Feb. 23, 1952, a spinal fusion was carried out and a diagnosis of multiple myeloma was established. Further lesions developed in skull and ribs. On Oct. 26, 1953, the patient, now a paraplegic with complete destruction of the body of the third lumbar vertebra, and constant severe back pain, was transferred from another hospital for total body irradiation. On Nov. 11, 1953, with patient turned on her side in bed, she received 200 r (skin dose) to back (250 kv., half-value layer 1.8 mm. Cu, target skin distance 365 cm). There were two episodes of vomiting without nausea at four and six hours after treatment and minimal nausea but no further vomiting on the first and second post-treatment days. From the third treatment day there were no further symptoms of nausea and moderate pain relief was noted. Pain began to become more severe again after five weeks. On Dec. 16, 1953 (five weeks) the patient received another 100 r (skin dose) to the back under the same conditions as previously. There were no symptoms of nausea or vomiting, and again there was some reduction in back and leg pain. Pain was relieved for about one month and then recurred with the same severity as before treatment. For this reason a cervical cordotomy was planned, but the patient died at operation on Jan. 28, 1954.

An autopsy was performed. The tumor that had received intensive local irradiation showed

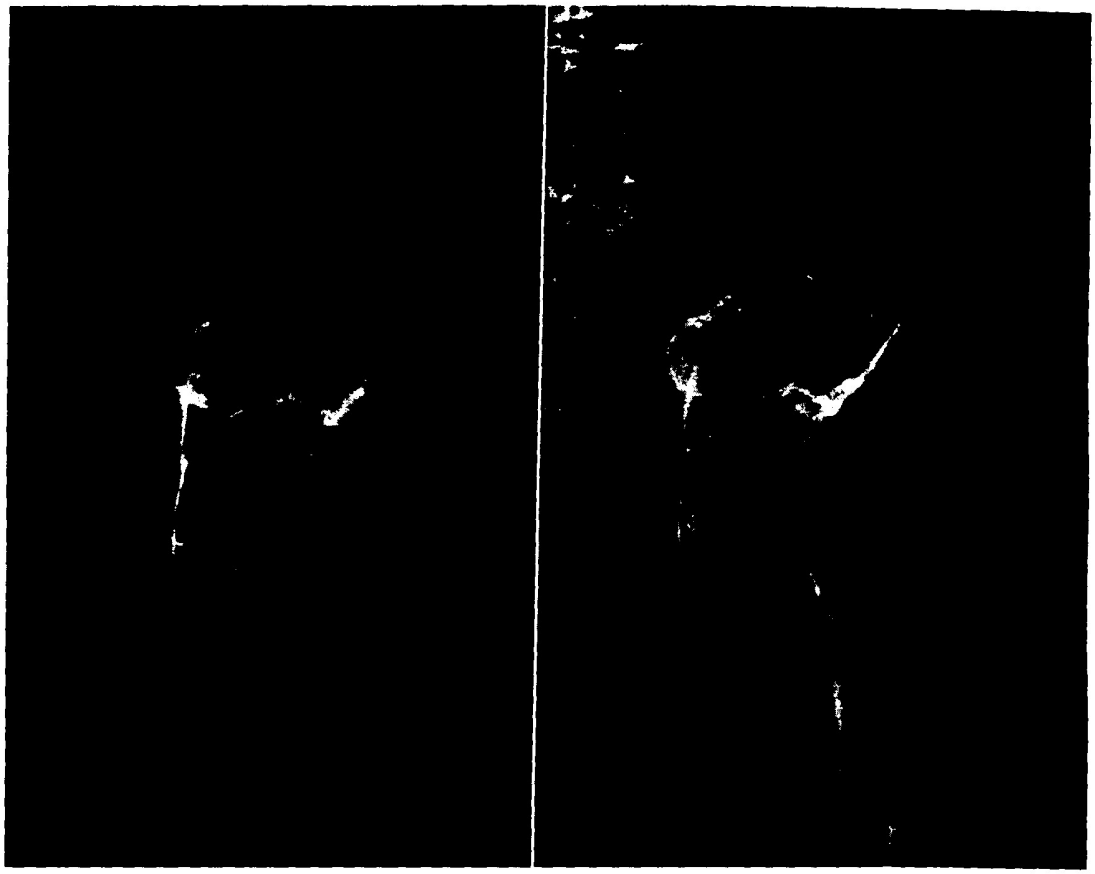

FIG. 1. Case v. J.C. The pelvis shows extensive involvement by multiple myeloma with biopsy defect and pathologic fracture involving the left ilium. The bone lesions showed no progress in the eight months following treatment.

histopathologic changes consistent with this treatment. Normal tissues that had been subjected to total body irradiation showed no gross or microscopic effects of such irradiation.

Laboratory data during the treatment period showed maximal depression from the 200 r dose.

	Initial	*Low*	*Final (7 wk.)*
Hb.	12.5 gm.	8.7 gm. @ 3 wk.	8.9 gm.
R.B.C.	4,000,000	2,700,000 @ 3 wk.	2,800,000
W.B.C.	11,000	2,600 @ 3 wk.	5,200
Platelets	150,000	50,000 @ 5 wk.	92,000

The differential white blood cell count at three weeks showed an increase in lymphocytes but the absolute lymphocyte count remained approximately constant.

CASE V. J.C. (AX-5284) A white male, aged thirty-five, had suffered a fracture of cervical spine in an accident three years previously and extensive lesions of multiple myeloma were discovered at that time. A year later the diagnosis was confirmed by biopsy. Except for a gradual weight loss of 45 pounds, the patient remained well, subjectively, until four months before admission. From this time he was confined to bed by severe back pain and increasing weakness. Roentgenograms showed compression fractures of several vertebral bodies and he was transferred to the hospital on a Stricker frame. On July 22, 1953, he received 200 r (skin dose)

total body irradiation (250 kv., half-value layer 2.3 mm. Cu, target skin distance 400 cm.). Immediately after treatment he vomited once without nausea. He ate his noon day meal two hours later and had no further reaction. Pain relief was evident the day following treatment, and by the third day appetite was improved. On Aug. 13, 1953, a second dose of 200 r, under the same conditions as the first, was administered. This time there was no nausea or vomiting and there were no new complaints. One week later he was completely relieved of back pain and was up and about the ward voluntarily. His only complaint was of pain in feet and ankles. There were no roentgen changes evident in the bones of this area and the pain apparently was due to ambulation after five months in bed. He received five transfusions of 500 cc. each during September and was then discharged home. He has received no further treatment and now talks hopefully of returning to work (Fig. 1).

Laboratory data during this period were as follows:

	Initial	*Low*	*Final (8 mo.)*
Hb.	8.3 gm.	6.0 gm. @ 5 wk.	11.0 gm.
R.B.C.	3,800,000	1,700,000 @ 5 wk.	3,200,000
W.B.C.	6,000	550 @ 5 wk.	8,250
Platelets	295,000	13,000 @ 6 wk.	210,000
Iron turnover half time	0.5 hr.	1.0 hr. @ 3 wk.	0.8 hr.

The differential white cell count at five weeks showed a doubling in the percentage of lymphocytes.

For both radiation therapy and chemotherapy, the ultimate effects are mediated by intracellular chemical changes. For this reason the two may be compared on terms of tolerance of the individual response of the disease, and factors governing their role in application.

Tolerance to radiation does not lend itself to ready measurement. In Court Brown's[3] series of 60 patients, he was able to define three phases of radiation sickness: (1) the latent period extending from the time of treatment to the onset of symptoms; (2) a period of acute disturbance lasting from one and one-half to four hours after the onset of symptoms; (3) recovery period extending as long as four or five days. The length of the latent period was inversely proportional to the period of acute symptoms and was used as an index of severity of reaction. In the patients presented here, a pattern of symptoms was not apparent; nausea and vomiting were inconstant and their condition before treatment was such as to mask any minor degree of weakness or lethargy. From a symptomatic point of view, the reaction to single doses up to 200 r was less than would be anticipated with conventional doses of nitrogen mustard, and the hematopoietic depression was acceptable as compared with this agent.

The response of the patients' disease can only be considered as indicative that total body irradiation in single doses up to 200 r has therapeutic possibilities. The tolerated dose is beyond that necessary or desirable for leukemia but is in the effective range for lymphosarcoma and multiple myeloma. The patient who received 200 r on two occasions in three weeks had a clinical response that could be described as impressive.

No agent currently in use for treatment of generalized cancer is offered with intent to cure. Even increased survival as a result of therapy is difficult to confirm. Under these circumstances the principal benefit of treatment is early relief of signs and symptoms and this benefit may be mitigated by the severity of side effects of treatment, prolongation of treatment or delayed response to treatment. In all these respects, the administration of single doses of total body irradiation has some advantage.

There is an additional advantage in the matter of dose. Prescription of radiation dose is unique in its precision. It is possible under controlled conditions to deliver a desired amount to any tissue or to calcu-

late what has been delivered to any site. To relate dose and effect, it is desirable to determine dose at the site where effect is produced, so that a given result can be repeated or modified. Prescription of dose of pharmaceutical agents is usually on the basis of body weight, administered intravenously, orally, or intramuscularly. In the processes of absorption, dilution and transportation, the amount of the agent finally producing an intracellular chemical effect must be subject to wide and unpredictable variations. If the clinically effective dose closely approaches the tolerance dose, it is desirable to have knowledge and control of the amount of concentration of an agent at the cellular level where its effect is exerted.

SUMMARY

Total body irradiation in a single exposure up to 200 roentgens of 250 kilovolt roentgen rays may be safely administered to patients with generalized cancer. Considered as one form of systemic therapy rather than as an alternative or competitive method of treatment, total body irradiation in doses of this order is a useful addition to the management of advanced cancer.

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